

Original Article**Novel cardiovascular risk factors in metabolic syndrome with and without coronary artery disease**

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ABSTRACT

Background: India is home to one of the largest population of people with metabolic syndrome (MetS) which is a cardiovascular diseases (CVDs) risk factor. So there is a surging interest in identifying novel risk factors which could be helpful in preventing future morbidity and mortality and thereby reducing the burden of CVDs.

Aims: Aim of the current study was to determine the levels of novel risk factors namely hsCRP, ferritin, Lp (a) and uric acid (UA) in MetS subjects with and without coronary artery disease (CAD) and find out their association with components of MetS as well as other traditional risk factors.

Material & Methods: 150 subjects participated in the study. They were divided as Group I: fifty healthy controls, Group II: fifty MetS subjects without CAD and Group III: fifty MetS subjects with CAD. After clinical examination and anthropometric measurements, overnight fasting blood samples were collected for biochemical analysis.

Results: The novel CAD risk factors (hsCRP, ferritin Lp (a) and UA) were significantly higher in gr.III as compared to gr.II ($p < 0.05$). The Pearson's coefficient at 95 % confidence interval showed positive correlation of ferritin, hsCRP, Lp (a) and UA with other CVD risk factors. They negatively correlated with HDL-C.

Conclusions: This highlights a significant association of the novel cardiovascular risk factors notably ferritin, hsCRP, Lp (a) and UA in MetS subjects with CAD compared to traditional risk factors like TGs, WC and TC suggestive of their usefulness as markers.

Key words: Coronary artery disease, metabolic syndrome, hsCRP, ferritin, Lipoprotein (a)

INTRODUCTION

Asian Indians are known to be at a high risk for type-2-diabetes mellitus (T2DM), cardiovascular disease (CVD) and metabolic syndrome (MetS) which is attributed to the 'Asian phenotype' [1,2]. CVDs are accompanied by the elevation of several positive acute phase reactants such as C-reactive protein (CRP) and ferritin [3]. CAD (a CVD) includes a spectrum of disease manifestation ranging from asymptomatic atherosclerotic disease to acute coronary syndrome comprising myocardial infarction (MI) and angina. The MetS is closely linked to insulin resistance (IR) and numerous studies indicate a link to iron overload. Increased serum ferritin is often associated with measures of IR, such as elevated blood glucose and insulin levels [4, 5]. The

association of high iron stores and CAD was first suggested by Sullivan [6]. However the association between elevated iron stores and the MetS has been less well explored. CRP, another molecule, is a marker of subclinical inflammation that predicts the occurrence of CAD in healthy subjects. Several studies have reported that subjects with MetS have a higher high sensitivity CRP (hsCRP) level than those without it [7-9]. Lipoprotein (a) [Lp(a)], considered an emerging risk factor by National Cholesterol Education Programme's Adult Treatment Panel III (NCEP ATP III), has been implicated in the development of the premature atherosclerotic disease seen in South Asians [10]. Serum uric acid (UA) is implicated as one of the potential risk factors underlying the development of both MetS and CVDs. Uric acid has often been considered as a part of

MetS, CAD and its risk factors [11,12]. Indians are at a higher risk of developing CAD than other races and this cannot be explained by traditional risk factors alone. Keeping this background in mind the main objective of the present study was to determine the levels of novel risk factors viz; hsCRP, ferritin, Lp(a) and UA in MetS subjects with and without CAD.

MATERIAL AND METHODS

This study was carried out at the Guru Gobind Singh Government Hospital (GGGH), Jamnagar after prior approval from Institutional Ethics Committee. The study population comprised of Group I, Group II and Group III. Group I comprised of fifty healthy controls. Group II consisted of fifty MetS subjects without CAD while Group III comprised of fifty MetS subjects with CAD. All the participants of the study were selected by employing inclusion and exclusion criteria.

Inclusion criteria for MetS were subjects having any three of the following:

1. Waist circumference (WC) ≥ 90 cm for Asian men or ≥ 80 cm for Asian women),
2. Triglycerides (TGs) ≥ 150 mg/dl,
3. High density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dl for men or ≤ 50 mg/dl for women,
4. Systolic/diastolic blood pressure $\geq 130/85$ mmHg or receiving drug treatment, and
5. Fasting plasma glucose (FBS) ≥ 100 mg/dl or receiving drug treatment.

The subjects of Group III were selected based on criteria for MetS and as well as those having signs and symptoms of MI & Angina, clinical examination, electrocardiogram readings, angiographic evidence and measurement of cardiac enzymes.

Exclusion criteria were:

1. Subjects having infectious disease, arthritis, renal failure, malignancy, liver disease, rheumatic fever, blood diseases such as leukaemia,
2. Pregnant women, Subjects receiving statin drugs, antibiotics, corticosteroids, immunosuppressive therapy and estrogen.
3. Subjects were excluded if they had high ferritin levels like haemochromatosis, liver disease, tuberculosis, chronic inflammatory diseases, those on iron therapy and those having past history of AMI or CHD.

An informed consent was signed by subjects willing to participate in the study. All the participants underwent

clinical examination including anthropometric measurements and biochemical investigations. The anthropometric measurements comprised of WC, height and body weight. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2). WC was determined by applying a tape measure to the midpoint between the inferior margin of the last rib and the crest of the Ilium. Blood pressure was measured using a sphygmomanometer with the patient in the sitting position.

Biochemical analysis: A twelve hours overnight fasting 5 ml blood samples were collected for the analysis of various biochemical parameters. All biochemical parameters were analyzed on fully automated analyzer in clinical biochemistry laboratory of GGGH. Quantitative estimation of glucose, total cholesterol (TC), TGs, HDL-C and low density lipoprotein cholesterol (LDL-C) were determined by using commercially available kits. Very low-density lipoprotein cholesterol (VLDL-C) was calculated by dividing the value of TG by 5. Immunoturbidimetric assay was employed for serum hsCRP levels and ferritin. Lp(a) levels were determined by the latex turbidimetric method. Elevated hsCRP levels refer to levels above 3 mg/L. Elevated ferritin refers to serum levels above 200 $\mu\text{g/L}$. Elevated Lp (a) levels refer to serum levels above 20 mg/dl. Elevated UA levels refer to serum levels above 7 mg/dl in men and above 6 mg/dl in women.

Statistical Analysis: Data were analyzed using software PRISM version 6. The values are expressed as a mean \pm S.E. Student's t-test was used for the intergroup comparisons. Chi square analysis was used to compare proportions. Pearson correlation coefficient determination was done to evaluate the degree of association of serum ferritin, hsCRP, Lp(a) and UA with all CVD risk factors. P-value < 0.05 was considered significant.

RESULTS

A total of 150 subjects participated in this study. The acquired results of the data of our study indicated that among 150 subjects, 74 (49.33 %) and 76 (50.66%) were female and male respectively. The mean age of controls and cases was similar (Group I: 49 ± 1.13 ; Group II: 48.74 ± 0.88 and Group III: 50.26 ± 1.098), age ranging between 30–60 years. Table-1 shows demographic characteristics of the study population. 100 participants were diagnosed of MetS. Table-2 gives a comparison of MetS components and CVD risk factors between study groups. The mean of all

components of MetS and CVD risk factors are significantly higher in group II & III compared to group I.

Table 1: Demographic characteristics of the study population

	Females (N= 74) N (%)	Males (N=76) N (%)	Total N (%)
Gender	74 (49.33)	76 (50.66)	150 (100)
Age Group (years)			
30-45	28 (18.67)	23 (15.33)	51 (34)
46-60	46 (30.66)	53 (32.66)	99 (69.33)
Addiction			
Yes	71 (47.33)	18 (12)	89 (59.33)
No	3 (2)	58 (38.67)	61 (40.67)
Dietary Habit			
Veg	66 (44)	63 (42)	129 (86)
Non veg	8 (5.33)	13 (8.67)	21 (14)
Lifestyle:			
Sedentary	14 (9.33)	10 (6.66)	24 (16)
Mild	45 (30)	46 (30.66)	91 (60.67)
Moderate	15 (10)	20 (13.33)	35 (23.33)
BMI (Kg/mt²):			
Normal (18.5-22.9)	28 (18.67)	32 (21.33)	60(40)
Over Weight (23-24.9)	21 (14)	18 (12)	39 (26)
Obese (≥ 25)	24 (16)	26 (17.33)	50 (34)
Diagnosis:			
HTN	30 (40.50)	39 (51.31)	69 (46)
MetS*	44(29.33)	56 (37.33)	100(66.7)
Angina	18(12)	10(6.66)	28(18.67)
MI	2 (1.33)	20(13.33)	22(14.67)
None	30 (20)	20 (13.33)	50(33.33)
MetS Components:			
WC (cm)			
< 80 in Females; < 90 in Males	11 (7.33)	27 (18)	38 (25.33)
≥ 80 in Females; ≥ 90 in Males	63 (42)	49 (32.67)	112 (74.67)
BP (mm of Hg)			
<130/85	39 (26)	31 (20.67)	70 (46.67)
$\geq 130/85$	35 (23.33)	45 (30)	80 (53.33)
FBS (mg/dl)			
< 100	40 (26.66)	41 (27.33)	81 (54)
≥ 100	34 (22.66)	35 (23.33)	69 (46)
TGs (mg/dl)			
< 150	47 (31.33)	42 (28)	89 (59.33)
≥ 150	27 (18)	34 (22.67)	61(40.67)
HDL-C (mg/dl)			

>50 in Females; >40 in Males	15(10)	41 (27.33)	56 (37.33)
≤ 50 in females ≤ 40 in Males	59 (39.33)	35 (23.33)	94 (62.67)
Novel Risk Factors of AMI:			
hs-CRP (mg/L)			
≤ 3 mg/dl	49 (32.66)	37 (24.66)	96 (64)
> 3mg/dl	25 (16.66)	39 (26)	54 (36)
Ferritin (μg/L)			
≤ 200	59 (39.33)	51 (30.66)	110 (73.33)
>200	15 (10)	25 (16.66)	40 (26.67)
Lp (a) {mg/dl}			
< 20	43 (28.67)	29 (19.33)	72 (48)
≥ 20	31 (20.67)	47 (31.33)	78 (52)
UA (mg/dl)			
≤ 6 in Females ; ≤ 7 in Males	42 (28)	41 (27.33)	83 (55.33)
> 6 in females; > 7 in Males	32 (21.33)	35 (23.33)	67(44.66)
*revised NCEP ATPIII modified criteria for South Asian population as proposed by the AHA/NHLB., 2005			

BMI: Basal metabolic rate; HTN: hypertension; MI: myocardial infarction; MetS: Metabolic Syndrome; WC: Waist Circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting Blood Sugar; TGs: Triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; hsCRP: high sensitivity C-reactive protein; Lp(a): Lipoprotein (a); UA: Uric Acid.

Between group II and III, all the MetS components were found significantly higher in group III except WC and TGs. All the CVD risk factors were significantly higher in group III as compared to group II except TC. The distribution of serum ferritin for each group is shown in figure 1. On doing Chi-square analysis, the novel CAD risk factors (hsCRP, ferritin, Lp(a) and UA) were significantly higher in cases as shown in figure 2. The correlation between ferritin, hsCRP, Lp(a) & UA with CVD risk factors was checked by Pearson's correlation coefficient at 95 % confidence interval depicted in table 3. hsCRP was found to be positively correlated with all the components except TC. Ferritin was found to be positively correlated with all the components except TC and TGs. Lp(a) was positively correlated with all the components except TC, TGs, LDL-C and VLDL-C. UA was found to be positively correlated with all the components except BMI, FBS, TC, and LDL-C. hsCRP, ferritin, Lp(a) and UA were negatively correlated with HDL-C.

Table 2: Comparison of MetS Components and CVD risk factors in cases and controls

Clinical & Biochemical Variables	Group I N=50			Group II N=50			Group III N=50		
	Mean (\pm SE)	Mean (\pm SE)	P value	Mean (\pm SE)	Mean (\pm SE)	P value	Mean (\pm SE)	Mean (\pm SE)	P value
Age (yrs)	49 (1.13)	48.74 (0.88)	0.868	49 (1.13)	50.26 (1.098)	0.347	48.74 (0.88)	50.26 (1.098)	0.349
BMI (kg/mt²)	21.44 (0.31)	24.56 (0.63)	<0.0001	21.44 (0.31)	26.57 (0.64)	<0.0001	24.56 (0.63)	26.57 (0.64)	0.0124
MetS components:									
WC (cm)	88.12 (0.32)	94.4 (1.57)	<0.0001	88.12 (0.32)	90.64 (1.034)	0.1713	94.4 (1.57)	90.64 (1.034)	0.0434
SBP (mmHg)	118 (0.56)	138.2 (2.78)	<0.0001	118 (0.56)	164.5 (2.733)	<0.0001	138.2 (2.78)	164.5 (2.733)	<0.0001
DBP (mmHg)	77 (0.555)	87.86 (1.24)	<0.0001	77 (0.555)	95.24 (1.11)	<0.0001	87.86 (1.24)	95.24 (1.11)	<0.0002
FBS (mg/dl)	83.93 (1.43)	195.1 (14.94)	<0.0001	83.93 (1.43)	106.4 (4.746)	<0.0001	195.1 (14.94)	106.4 (4.746)	<0.0001
TGs (mg/dl)	110.9 (3.84)	160.4 (8.7)	<0.0001	110.9 (3.84)	174.5 (6.148)	<0.0001	160.4 (8.7)	174.5 (6.148)	0.73
HDL-C (mg/dl)	46.61 (0.81)	43.24 (1.17)	0.0084	46.61 (0.81)	35.61 (1.048)	<0.0001	43.24 (1.17)	35.61 (1.048)	<0.0001
CVD Risk factors:									
TC (mg/dl)	170.3 (2.572)	162.9 (5.662)	0.0816	170.3 (2.572)	174.5 (6.148)	0.555	162.9 (5.662)	174.5 (6.148)	0.1988
LDL-C (mg/dl)	107.5 (1.83)	117.2 (4.97)	0.048	107.5 (1.83)	136.5 (6.743)	<0.0001	117.2 (4.97)	136.5 (6.743)	0.0356
UA (mg/dl)	5.31 (0.235)	6.9 (0.37)	<0.0001	5.31 (0.235)	8.14 (0.44)	<0.0001	6.9 (0.37)	8.14 (0.44)	0.0217
hsCRP (mg/l)	0.66 (0.03)	3.02 (0.31)	<0.0001	0.66 (0.03)	4.402 (0.26)	<0.0001	3.02 (0.31)	4.402 (0.26)	<0.0001
Ferritin(μg/L)	72 (4.5)	167.9 (18.84)	<0.0001	72 (4.5)	222 (14.43)	<0.0001	167.9 (18.84)	222 (14.43)	0.0118
Lp(a) (mg/dl)	13.05 (0.935)	26.05 (3.360)	0.001	13.05 (0.935)	39.98 (3.371)	<0.0001	26.05 (3.360)	39.98 (3.371)	<0.0001

Two-tailed paired t test, significantly different at (P < 0.05)

Values are expressed as Mean (\pm SE); Group I= Control; Group II= MetS-CAD; and Group III= MetS+ CAD.

DISCUSSION

Cardiovascular diseases (CVDs), comprising of coronary heart disease (CHD) and cerebro-vascular diseases, are currently the leading cause of death globally, accounting for 21.9 per cent of total deaths, and are projected to increase to 26.3 per cent by 2030 [13]. As the presence of MetS in CAD is not well explored in Indian population, the present work is an attempt to study novel risk factors of CAD and its association with MetS.

In the current study a higher prevalence rates of elevated ferritin, hsCRP, Lp(a) and UA in MetS subjects with CAD. The similar findings have been reported recently [14]. Solomen et al first reported a significant association between serum ferritin level and risk of MI where a value above 200 μ g/L had a 2.2 higher risk of MI than subjects with lower ferritin levels. Significantly higher serum ferritin levels in MetS subjects with CAD compared to others was seen in the current study. Elevated serum ferritin is a

marker of iron stores which may induce CAD as well as MetS through a variety of mechanisms including oxidative damage of pancreatic beta cells, impairment of hepatic insulin extracts by liver, suppressed hepatic glucose production and lipid peroxidation [15, 16]. This indicates that serum ferritin enhances the role of LDL-C in the induction of CVDs. This role is further enhanced by elevation of hsCRP [17].

CRP is known to be associated with diabetes and CVDs. Recent studies have shown that elevated CRP levels are associated with MetS. Several studies have also emphasized the concept that a proinflammatory state is one component of MetS. One of the possible mechanisms is that adipocytes in obese subjects with MetS release into the circulation high amounts of tumor necrosis factor-alpha and Interleukin-6 into the circulation which stimulates the production of hsCRP by the liver and induce IR.

Table 3: Association between hsCRP, ferritin, Lp(a) & UA with traditional CVD Risk Factors

Variables	CC* of hsCRP	P value	CC* of Ferritin	P value	CC* of Lp(a)	P value	CC* of UA	P value
BMI (kg/m ²)	0.33	<0.0001	0.2223	0.0063	0.235	0.0038	0.184	0.242
SBP(mmHg)	0.4633	<0.0001	0.337	<0.0001	0.3782	<0.0001	0.2861	0.0004
DBP (mmHg)	0.4384	<0.0001	0.2693	<0.0009	0.405	<0.0001	0.2539	0.0017
FBS (mg/dl)	0.5734	<0.0001	0.2569	<0.0016	0.241	0.0031	0.09328	0.2625
TC (mg/dl)	0.056	0.4934	0.03798	0.6445	-0.0709	0.3886	-0.1258	0.1252
TG (mg/dl)	0.3149	<0.0001	0.1457	0.0753	0.02735	0.7397	0.2355	0.0037
LDL-C(mg/dl)	0.1999	0.0142	0.195	0.0167	0.1005	0.221	0.03783	0.6458
HDL-C (mg/dl)	-0.04763	<0.0001	-0.4052	<0.0001	-0.2365	0.0036	-0.23035	0.0125
VLDL-C (mg/dl)	0.3149	<0.0001	0.1457	0.0753	0.02735	0.7397	0.03783	0.0753
UA (mg/dl)	0.2854	<0.0001	0.2801	0.0005	0.223	0.0063	--	--
Lp(a) (mg/dl)	0.2959	0.0002	0.2834	0.0004	--	--	0.2223	0.0063
hsCRP (mg/L)	--	--	0.6315	<0.0001	0.2959	0.0002	0.2854	0.0004
Ferritin (µg/L)	0.63	<0.0001	--	--	0.2834	0.0004	0.2801	0.0005

*CC: Correlation coefficient; Significance ($\alpha=0.05$), two tailed P value Correlation using Carl Pearson Technique (r), Confidence interval (CI) at 95%

IR itself is responsible for the higher level of cytokine production [18, 19]. A significant difference has been observed regarding the value of hsCRP in MetS subjects with CAD in this study indicating an association between hsCRP and CAD and these observations are similar to the previous studies [14]. CRP can be produced within the vascular smooth muscle of diseased coronary arteries and this production may directly lead to the expression of several mediators of the atherothrombotic process [20, 21].

Lp(a) is now considered as one of the novel CAD risk factors. Lp(a) levels above 20 and 30 mg/dl for south asian and western population respectively are commonly accepted cut-off points for categorizing high plasma Lp(a). Subjects with Lp(a) above these

cut-off points have their risk of CAD increased by about three-fold than those with low plasma Lp(a) [22]. We studied Lp(a) levels which was found significantly higher in MetS subjects with CAD. Serum levels of Lp(a) have been shown to correlate with the presence, extent and severity of CAD as well as occurrence and recurrence of MI and cardiac deaths [23].

Elevated serum UA levels have been associated not only with the components of MetS but also found to be predictors of CVDs in non diabetics as well as those with T2DM [24, 25]. In our study we also found UA higher in MetS subjects with CAD. It has been earlier reported that UA promotes LDL-C oxidation and is involved in the progression of atherosclerosis [24].

Figure 1: Distribution of serum Ferritin

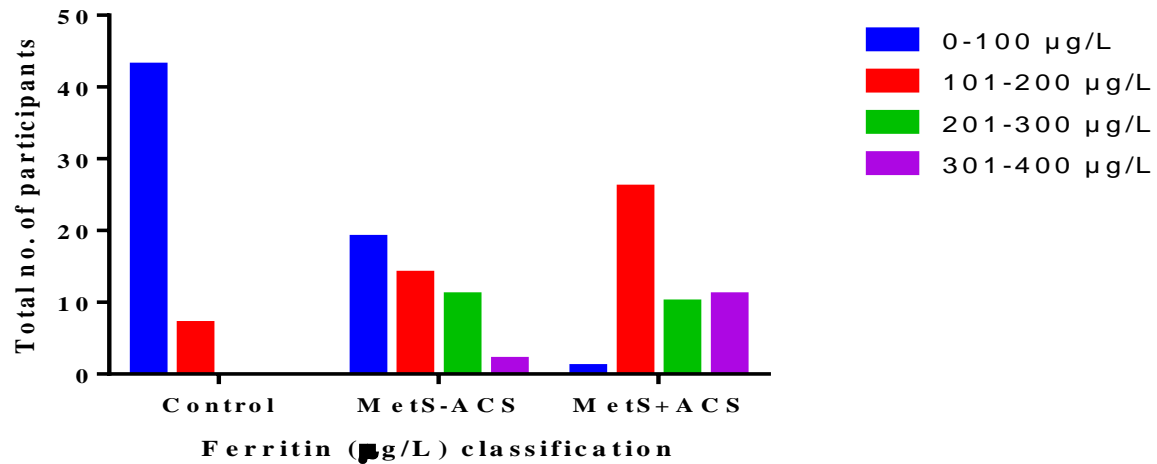
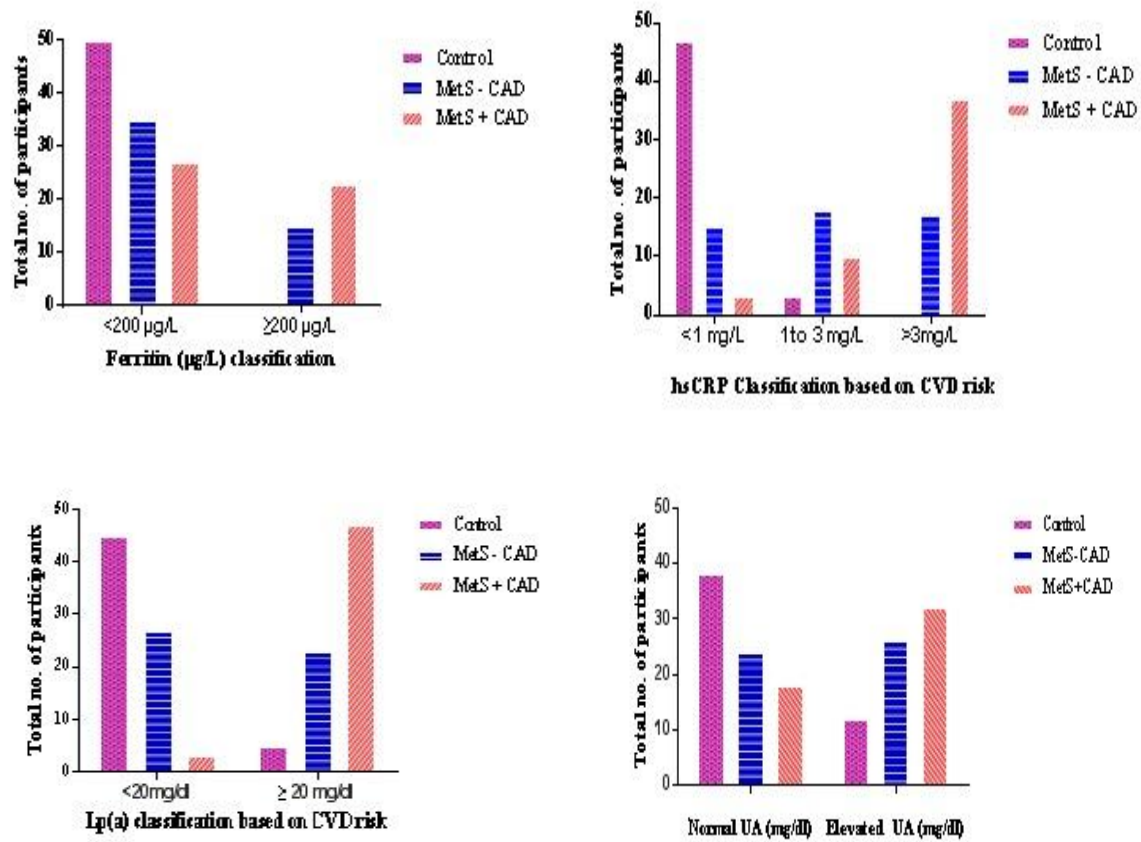


Figure 2: Distribution of Ferritin, hsCRP, Lp (a) and UA in study groups based on CVD risk classification



Elevated serum UA levels have been associated not only with the components of MetS but also found to be predictors of CVDs in non diabetics as well as those with T2DM [24, 25]. In our study we also found UA higher in MetS subjects with CAD. It has been earlier reported that UA promotes LDL-C oxidation and is involved in the progression of atherosclerosis [24].

CONCLUSION

We found a significant association of the novel cardiovascular risk factors notably ferritin, hsCRP, Lp(a) and UA in MetS subjects with CAD compared to traditional risk factors like TGs, WC and TC. We conclude that the inclusion of assessment of these novel cardiovascular risk factors in MetS subjects may prove better predictors of future cardiovascular events. These may therefore prove to be valuable to the clinicians in preventing future morbidity and mortality due to CVDs.

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